SUNFISH Parts 1 and 2: 4-year efficacy and safety of risdiplam in Types 2 and 3 spinal muscular atrophy (SMA)

Laurent Servais,1-3* Maryam Oskoui,4 John W Day,5 Nicolas Deconinck,6,7 Elena S Mazzone,8 Andres Nascimento,9 Kayoko Saito,10 Carole Vuillerot,11,12 Giovanni Baranello,13,14 Odile Boespflug-Tanguy,1,15 Nathalie Goemans,16 Janbernd Kirschner,17 Anna Kostera-Pruszczyn,18 Jessica Braid,19 Gergely Papp,20 Ksenija Gorni,21 Carmen Martin,19 Wai Yin Yeung,19 Eugenio Mercuri,8 on behalf of the SUNFISH Study Group

1IMotion Institut de Myologie AP-HP, Hôpital Armand Trousseau, Paris, France; 2MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, UK; 3Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Liège, Belgium; 4Departments of Pediatrics and Neurology Neurosurgery, McGill University, Montreal, Canada; 5Department of Neurology, Stanford University, Palo Alto, CA, USA; 6Centre de Référence des Maladies Neuromusculaires, Children’s University Hospital, ULB, Brussels, Belgium; 7Neuromuscular Center, UZ Gent, Ghent, Belgium; 8Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy; 9Neuromuscular Unit, Neuropaediatrics Department, Hospital Sant Joan de Déu, Fundacion Sant Joan de Déu, CIBERER – ISC III, Barcelona, Spain; 10Medical Genetics Institute, Tokyo Women’s Medical University, Tokyo, Japan; 11Service de Rééducation Pédiatrique Infantile “L’Escale”, Hôpital Femme Mère Enfant, CHU-Lyon, Bron, France; 12Neuromyogen Institute, CNRS UMR 5310 - INSERM U1217, Université de Lyon, Lyon, France; 13The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust, London, UK; 14Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; 15Université Paris Cité, UMR 1141, NeuroDiderot, Paris, France; 16Neuromuscular Reference Centre, Department of Paediatrics and Child Neurology, University Hospitals Leuven, Leuven, Belgium; 17Department of Neuropediatrics and Muscle Disorders, Medical Center-University of Freiburg, Freiburg, Germany; 18Department of Neurology, Medical University of Warsaw, Warsaw, Poland; 19Roche Products Ltd, Welwyn Garden City, UK; 20Pharma Development, Safety, F. Hoffmann-La Roche Ltd, Basel, Switzerland; 21PDMA Neuroscience and Rare Disease, F. Hoffmann-La Roche Ltd, Basel, Switzerland.

*Presenter
Disclosures

- LS is a PI of SMA studies for F. Hoffmann-La Roche Ltd, Biogen, and AveXis; he has attended SAB of F. Hoffmann-La Roche Ltd, Biogen and AveXis and received consultancy fees from Biogen; he serves on the board for Cytokinetics; he is co-inventor in the patent 20190029605 (Method for estimating physical activity of the upper limb) from which he has not perceived any financial interest
- MO is a PI of SMA studies for F. Hoffmann-La Roche and Biogen
- JWD reports grants from: AMO Pharmaceuticals, aTyr, AveXis, Biogen, Bristol Meyers Squibb, Cytokinetics, Ionis Pharmaceuticals, Roche Pharmaceuticals, Sanofi-Genzyme and Sarepta Therapeutics; he has served as a consultant for: AMO Pharmaceuticals, AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Roche Pharmaceuticals, Pfizer, Sarepta Therapeutics and Santhera Pharmaceuticals; he has patents licensed to Athena Diagnostics for genetic testing of myotonic dystrophy Type 2 (US patent 7442782) and spinocerebellar ataxia type 5 (US patent 7527931)
- ND is a PI of SMA studies for F. Hoffmann-La Roche, Novartis, Biogen and AveXis. He has received consultancy fees from F. Hoffmann-La Roche, Biogen and AveXis
- ESM is a master trainer for SMA studies and receives consultancy fees from AveXis, Biogen, F. Hoffmann-La Roche and Scholar Rock
- AN is a PI of SMA studies for F. Hoffmann-La Roche, Biogen and Scholar Rock; he has received consultancy fees from F. Hoffmann-La Roche, Biogen, Scholar Rock and AveXis
- KS has attended advisory boards for Biogen, Novartis Pharma and Roche/Chugai; she is a consultant for AveXis and has received research funding from AveXis/Novartis, Biogen and Roche/Chugai for research consultation for execution of clinical trial projects and from Ionis Pharmaceuticals for execution of clinical trial projects
- CV is a PI of SMA studies for F. Hoffmann-La Roche; she has attended SAB of Roche, Biogen and AveXis and received consultancy fees from F. Hoffmann-La Roche
- GB has received speaker and consultancy honoraria from AveXis, Inc., Roche, PTC and Sarepta Therapeutics
- OBT is a PI of studies for F. Hoffmann-La Roche, AveXis, Santhera, Italfarmaco, Ultragenyx and Metfora; she is a DSMB member for Inventiva and Minoryx Therapeutics
- NG is a PI of SMA studies for F. Hoffmann-La Roche; she has received consultancy fees from F. Hoffmann-La Roche, Biogen and AveXis
- JK has received honoraria for clinical research and/or consultancy activities from Biogen, Novartis Gene Therapies, Roche and Scholar Rock
- AKP is a PI of SMA studies for F. Hoffmann-La Roche; she has attended advisory boards of Biogen, PTC Therapeutics and AveXis, received speaker honoraria from Biogen and PTC Therapeutics and grant support from Biogen
- JB, GP, KG, CM and WYY are employees of, and hold shares in, F. Hoffmann-La Roche Ltd
- EM receives fees from AveXis, Biogen and F. Hoffmann-La Roche

This study was sponsored by F. Hoffmann La Roche Ltd, Basel, Switzerland. Writing and editorial assistance was provided by Lynsey Forsyth, PhD, of Nucleus Global, in accordance with Good Publication Practice (GPP 2022) guidelines (http://www.ismpp.org/gpp-2022)
Introduction

- SMA is a severe, progressive neuromuscular disease leading to loss of motor function and reduced life expectancy\(^1\)
- Risdiplam is a centrally and peripherally distributed oral SMN2 pre-mRNA splicing modifier that increases and sustains the levels of functional SMN protein\(^2\)–\(^5\) and has been approved for the treatment of patients with SMA in over 90 countries worldwide\(^6\)
- SUNFISH (NCT02908685) is a two-part clinical trial of risdiplam in a broad and heterogeneous patient population with Types 2 and 3 SMA (aged 2–25 years)\(^7\)
  - Part 1 was a dose-finding study, which determined the dose for Part 2
  - Part 2 is the confirmatory study assessing the efficacy of risdiplam at the dose selected in Part 1
- The primary outcome of Part 2 was met, showing a statistically significant difference in the change from baseline in MFM32 total score at Month 12 in patients treated with risdiplam (n=120) versus placebo (n=60)\(^8\)
- Without treatment, patients with Types 2 and 3 SMA show a decline in MFM32, RULM and HFMSE scores over time\(^9\)–\(^11\)
- Here we present efficacy and safety data from patients who have received long-term risdiplam treatment for 4 years (48 months)

---

A randomized, placebo-controlled, double-blind study with broad inclusion criteria and a large dataset

Part 1 primary objective: To evaluate the safety, tolerability, PK and PD of risdiplam, and to select the dose for Part 2

Part 2 primary endpoint: Change from baseline in MFM32 total score at Month 12

Exploratory efficacy analyses at Month 48:
- Change from baseline in MFM32 total score
- Percentage of patients who achieve stabilization or improvement (≥0) or a change of ≥3 from baseline in MFM32 total score
- Change from baseline in RULM total score
- Change from baseline in HFMSE total score
- Change from baseline in SMAIS-ULM total score (patient and caregiver report)

Safety:
- Most common AEs and SAEs from baseline to Month 48
- Rate of AEs and SAEs per 100PY over 48 months

*Non-ambulant is defined as not having the ability to walk unassisted for ≥10m. †RULM entry item A (Brooke score) ≥2; ability to sit independently (≥1 on item 9 of the MFM32). ‡Except in the 1 year preceding screening or planned within the next 18 months.

AE, adverse event; HFMSE, Hammersmith Functional Motor Scale – Expanded; MFM32, 32-item Motor Function Measure; PD, pharmacodynamics; PK, pharmacokinetics; PY, patient years; RULM, Revised Upper Limb Module; SAE, serious AE; SMA, spinal muscular atrophy; SMAIS-ULM, SMA Independence Scale–Upper Limb Module.

SUNFISH has a diverse patient population including patients with contractures, severe scoliosis and low baseline motor function scores

<table>
<thead>
<tr>
<th>Patient baseline characteristics</th>
<th>Part 1 (N=51)</th>
<th>Part 2</th>
<th>Total (N=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risdiplam (n=120)</td>
<td>Placebo* (n=60)</td>
<td></td>
</tr>
<tr>
<td>Age at screening, years, median (range)</td>
<td>7 (2–24)</td>
<td>9 (2–25)</td>
<td>9 (2–24)</td>
</tr>
<tr>
<td>Age at onset of symptoms, months, mean (SD)</td>
<td>15.6 (10.6)</td>
<td>14.1 (8.4)</td>
<td>18.5 (21.1)</td>
</tr>
<tr>
<td>Gender, female/male, n (%)</td>
<td>27 (53)/24 (47)</td>
<td>61 (50.8)/59 (49.2)</td>
<td>30 (50.0)/30 (50.0)</td>
</tr>
<tr>
<td>SMA type, n (%)</td>
<td>2</td>
<td>37 (73)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>SMN2 copy number, n (%)</td>
<td>2</td>
<td>1 (2)</td>
<td>46 (90)</td>
</tr>
<tr>
<td>Scoliosis, n (%)</td>
<td>Yes &gt;40° curvature</td>
<td>29 (57)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>MFM32 total score, mean (SD)</td>
<td>42.9 (15.0) †</td>
<td>45.48 (12.09) ‡</td>
<td>47.35 (10.12) §</td>
</tr>
<tr>
<td>RULM total score, mean (SD)</td>
<td>18.47 (8.24) †</td>
<td>19.65 (7.22) †‡</td>
<td>20.91 (6.41) **</td>
</tr>
<tr>
<td>HFMSE total score, mean (SD) ‡‡</td>
<td>17.45 (16.92)</td>
<td>16.10 (12.46)</td>
<td>16.62 (12.09)</td>
</tr>
<tr>
<td>Patients with HFMSE total score &lt;10, n (%)</td>
<td>23 (45)</td>
<td>49 (41)</td>
<td>25 (42)</td>
</tr>
</tbody>
</table>

*Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 36 months. †n=44; adjusted baseline prior to first dose of risdiplam following placebo period. Part 1 only. ‡n=59. §n=59. †n=174. ††n=119.

**n=58. †‡n=177. †‡Based on enrollment criteria, at least 56% of patients in SUNFISH Part 2 would have been ineligible for the CHERISH trial (CHERISH inclusion criteria included: aged 2–12 years, baseline HFMSE score ≥10; and exclusion criteria included: severe scoliosis (>40° curvature). This percentage does not take into consideration patients with severe contractures (CHERISH exclusion criteria included any contracture that, according to the investigator, could interfere with the HFMSE). 14% of patients in Part 1 were ambulant. Data cut-off: 30 Sep 2020.

HFMSE, Hammersmith Functional Motor Scale – Expanded; MFM32, 32-item Motor Function Measure; RULM, Revised Upper Limb Module; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
Following an initial increase over 12 months the change from baseline in MFM32 total score was generally stable over 36 months

A natural history cohort of patients aged 6–30 years showed a decline of −2.66 points in the MFM32 after 24 months.

*+−95% CI. ‡Baseline is the last measurement prior to the first dose of risdiplam or placebo. §Data cut-off: 6 Sep 2022. †Data cut-off: 6 Sep 2019. Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 36 months. Risdiplam period not shown in this graph. ‡Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients. CI, confidence interval; MFM32, 32-item MFM.

1. Roche data on file; courtesy of Association Institut de Myology; first presented at MDA 2021.
The increase in RULM total score from baseline over 24 months was sustained up to Month 48 with risdiplam treatment.
Change from baseline in HFMSE total score with risdiplam treatment over 48 months in SUNFISH contrasts with an overall decline in a natural history cohort.
Patients and caregivers reported stabilization or continuous improvements in the SMAIS-ULM total score change from baseline with risdiplam treatment over 48 months.

Patients and caregivers reported stabilization or continuous improvements in the SMAIS-ULM total score change from baseline with risdiplam treatment over 48 months.
SUNFISH Parts 1 and 2: the observed AE profile over 48 months was reflective of underlying disease

<table>
<thead>
<tr>
<th>SUNFISH Part 1 (N=51)</th>
<th>Number of AEs per 100PY (95% CI)</th>
<th>SUNFISH Part 2 (N=179)*</th>
<th>Number of AEs per 100PY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PY at risk</td>
<td>247.4</td>
<td>Total PY at risk</td>
<td>662.5</td>
</tr>
<tr>
<td><strong>AEs reported at a rate of ≥15 per 100PY</strong></td>
<td></td>
<td><strong>AEs reported at a rate of ≥11 per 100PY</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>59.8 (50.6–70.3)</td>
<td>Headache</td>
<td>39.9 (35.2–45.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34.4 (27.4–42.5)</td>
<td>Upper respiratory tract infection</td>
<td>25.4 (21.7–29.5)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>26.7 (20.6–34.0)</td>
<td>Nasopharyngitis</td>
<td>19.2 (16.0–22.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>17.8 (12.9–23.9)</td>
<td>Vomiting</td>
<td>16.0 (13.1–19.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17.8 (12.9–23.9)</td>
<td>Pyrexia</td>
<td>15.6 (12.7–18.9)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>14.6 (10.2–20.1)</td>
<td>Cough</td>
<td>9.8 (7.6–12.5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14.1 (9.9–19.7)</td>
<td>Diarrhea</td>
<td>9.8 (7.6–12.5)</td>
</tr>
<tr>
<td><strong>SAEs reported at a rate of ≥0.8 per 100PY</strong></td>
<td></td>
<td><strong>SAEs reported at a rate of ≥0.8 per 100PY</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.4 (0.9–5.3)</td>
<td>Pneumonia</td>
<td>4.7 (3.2–6.6)</td>
</tr>
<tr>
<td>Femur fracture</td>
<td>0.8 (0.1–2.9)</td>
<td>Gastritis</td>
<td>0.8 (0.3–1.8)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0.8 (0.1–2.9)</td>
<td>Pyrexia</td>
<td>0.8 (0.3–1.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.8 (0.1–2.9)</td>
<td>Upper respiratory tract infection</td>
<td>0.8 (0.3–1.8)</td>
</tr>
</tbody>
</table>

There have been no treatment-related AEs leading to withdrawal or treatment discontinuation

*Includes 120 patients in the risdiplam arm who have been treated with risdiplam for 48 months and 58 patients from the placebo arm who were switched to the risdiplam arm after 12 months and have been treated with risdiplam for 36 months. One patient randomized to placebo was withdrawn prior to receiving any risdiplam dose.

Data cut-off: 6 Sep 2022.

AE, adverse event; CI, confidence interval; PY, patient years; SAE, serious AE.
SUNFISH Parts 1 and 2: overall rate of AEs and SAEs per 100PY

The overall rate of AEs per 100PY decreased over 48 months in SUNFISH Parts 1 and 2*.

Data cut-off: 6 Sep 2022.

AE, adverse event; CI, confidence interval; PY, patient years; SAE, serious AE.

*Includes 51 patients from Part 1 and 179 patients from the risdiplam and placebo/risdiplam arms in Part 2 (one patient randomized to placebo was withdrawn prior to receiving any risdiplam dose). †+/- 95% CI.
Part 1

Adherence/dose intensity†, mean % (95% CI)

99.4
(80.0–100.0)

Proportion of patients with adherence/dose intensity† ≥80%

98

Part 2*

Adherence/dose intensity†, mean % (95% CI)

98.7
(34.7–127.4)

Proportion of patients with adherence/dose intensity† ≥80%

98.3

*Treatment adherence was high in SUNFISH Parts 1 and 2.

*Includes 120 patients in the risdiplam arm who have been treated with risdiplam for 48 months and 58 patients from the placebo arm who were switched to the risdiplam arm after 12 months and have been treated with risdiplam for 36 months. One patient randomized to placebo was withdrawn prior to receiving any risdiplam dose.

†Dose intensity is the total number of doses actually received divided by the total number of planned doses, expressed as a percentage. Data shown are from first dose of risdiplam until data cut-off of 6 Sep 2022.

CI, confidence interval.
Conclusions

Increases in motor function scores observed in the first year of risdiplam treatment were sustained after 4 years.

Patients and caregivers reported continuous improvement or stabilization in the level of help needed for activities of daily living.

AEs and SAEs were reflective of underlying disease. The overall rate of AEs decreased over 48 months.

These results confirm the longer-term efficacy and safety of risdiplam in a broad and heterogeneous population of individuals with Type 2 and non-ambulant Type 3 SMA.
Acknowledgments

Many thanks to all the patients who participate in these studies, their families, healthcare professionals and the support of patient groups throughout the world.
A total of 8% (14/180) of patients discontinued from SUNFISH Part 2 over 48 months.

* Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 36 months.
† Two patients in the risdiplam arm switched to nusinersen (SPINRAZA®) treatment.
‡ This patient withdrew from the study to start nusinersen treatment.

Data cut-off: 6 Sep 2022.

A total of 8% (14/180) of patients discontinued from SUNFISH Part 2 over 48 months.
In SUNFISH Part 1, increases in MFM32 total score from baseline were maintained between Months 12 and 48 in patients treated with risdiplam.

*+/- 95% CI. †Data cut-off: 6 Sep 2022. ‡Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients. Excludes seven patients who performed the MFM20 assessment at baseline.

CI, confidence interval; MFM, Motor Function Measure; MFM20, 20-item MFM; MFM32, 32-item MFM.
Key demographic variables in SUNFISH Part 2 and the PNCR Network population

<table>
<thead>
<tr>
<th></th>
<th>SUNFISH Part 2 (risdiplam arm) n=120</th>
<th>PNCR(^1) n=91*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female/male, n (%)</td>
<td>51/49</td>
<td>42/58</td>
</tr>
<tr>
<td>Ethnicity, Asian/white/black or African American, %</td>
<td>19/67/2</td>
<td>11/68/0</td>
</tr>
<tr>
<td>Age at enrollment/screening, years, median (IQR)</td>
<td>9 (5–14)</td>
<td>8 (4–14)</td>
</tr>
<tr>
<td>Age at onset of symptoms, months, mean (SD)</td>
<td>14 (8)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Type 2 SMA, %</td>
<td>70</td>
<td>78</td>
</tr>
<tr>
<td>SMN(^2) copy number 2/3, %</td>
<td>3/89</td>
<td>5/91</td>
</tr>
<tr>
<td>HFMSE total score at baseline, mean (SD)</td>
<td>16.1 (12.5)</td>
<td>12.9 (10.9)</td>
</tr>
<tr>
<td>Patients with HFMSE total score &lt;10, %</td>
<td>41</td>
<td>51</td>
</tr>
<tr>
<td>Scoliosis, %</td>
<td>63 (75% of data missing)</td>
<td>13</td>
</tr>
</tbody>
</table>

*Includes participants from the PNCR network with the following criteria: HFMSE data at baseline, aged 2–25 years at enrollment, with Type 2 or 3 SMA who were non-ambulant (HFMSE Item 20 score = 0; if missing then Highest Current Level of Mobility criteria = none; if Highest Current Level of Mobility Criteria is missing then: Type 2 SMA who never walked without support or Type 3 who never walked without support and wheelchair use full time) at baseline and treatment naïve. Sample size is n=91 except for ethnicity (n=37), age of onset (n=78), SMN\(^2\) copy number (n=66) and scoliosis (n=23). Missing values are excluded from denominator.

HFMSE, Hammersmith Functional Motor Scale – Expanded; IQR, interquartile range; PNCR, Paediatric Neuromuscular Clinical Research Network; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival of motor neuron.